Amendments to the Claims:

1. (Withdrawn) A method of making a reference library comprising a mixture of heterogeneous nucleic acid fragments, comprising:

digesting pooled nucleic acids comprising first restriction sites with a first restriction endonuclease to produce a mixture of restriction fragments;

forming a first population of single stranded nucleic DNA fragments from a first subpopulation of said restriction fragments, wherein said first subpopulation of restriction fragments comprises a second restriction site which is different from said first restriction site;

forming a second population of single stranded DNA fragments from a second subpopulation of said restriction fragments wherein said second subpopulation of said restriction fragments do not contain said second restriction site, and wherein said first single stranded DNA fragments have complementary sequences to said second single stranded DNA fragments from said second subpopulation when said single stranded DNA fragments are derived from the same restriction fragment;

hybridizing the first and second populations of single stranded DNA fragments to form a first population of duplexes;

treating said first population of duplexes with a single strand dependent nuclease to digest mismatched duplexes in said first population.

2. (Withdrawn) The method of claim 1, further comprising:

reannealing intact single stranded DNA from said nuclease digestion to form a second population of duplexes; and

isolating said second population of duplexes to form a reference population of restriction fragments.

3. (Withdrawn) The method of claim 1, further comprising the step of amplifying the matched duplexes using PCR.

4. (Withdrawn) The method of claim 1, wherein said single strand dependent nuclease is selected from the group consisting of T7 endonuclease, S1 nuclease and mungbean nuclease.

5. (Withdrawn) The method of claim 1, wherein said single strand dependent nuclease is T7 endonuclease.

6. (Withdrawn) The method of claim 2, wherein said population of duplexes is isolated using biotin precipitation.

7. (Currently amended) A method of making a reference library comprising a mixture of heterogeneous nucleic acid fragments which has been enriched for polymorphic sequences, the method comprising:

(a) digesting pooled genomic nucleic acid from a population of individuals with a first restriction endonuclease, whose recognition site and cleavage site are coextensive, to produce a first mixture of restriction fragments having first cleavage ends with predictable protruding strands;

(b) ligating an Exo III resistant linker~~, comprising a 3' overhang,~~ to the first cleavage ends of said restriction fragments, to form a first ligation product population,

wherein said Exo III resistant linker comprises at one terminus a protruding strand which hybridizes to that of said first cleavage ends, and further comprises, at its opposite terminus, a 3'-overhang;

(c) digesting said first ligation product population with a second restriction endonuclease, whose recognition site and cleavage site are coextensive, ~~having a cleavage site different from that of said first restriction endonuclease~~ wherein the second restriction endonuclease is different from said first restriction endonuclease, and is selected such that the frequency of its restriction sites in the pooled genomic nucleic acid is less than that of the restriction sites of the first restriction endonuclease;

to form a second mixture of restriction fragments, wherein those fragments produced by cleavage with said second restriction endonuclease have a second cleavage end, having a protruding strand;

(d) ligating an Exo III susceptible linker, comprising either a 5'-overhang or a blunt end, and to each said second cleavage end, such that each said fragment produced by cleavage with

said second restriction endonuclease bears an Exo III susceptible terminus selected from said 5'-overhang and said blunt end,

~~to form~~ thereby forming a second ligation product population,

wherein said Exo III susceptible linker comprises a first member of a binding pair;

(e) digesting said second ligation product population with Exo III to form a third ligation product population, comprising (i) single stranded DNA comprising end sequences corresponding to said Exo III resistant and Exo III susceptible linkers and (ii) double stranded DNA comprising end sequences corresponding to said Exo III resistant linkers;

(f) denaturing said third ligation product population and hybridizing the mixture so obtained to form a reannealed third ligation product population; and

(g) contacting said reannealed third ligation product population with a second member of said binding pair to isolate duplexes containing said Exo III susceptible linker, thereby to enrich for duplexes which form a polymorphic reference population of restriction fragments.

8. (Currently amended) The method of claim 7, further comprising contacting said reannealed third ligation product with a single strand dependent nuclease, to digest mismatched duplexes.

9. (Previously presented) The method of claim 7, further comprising contacting said reannealed third ligation product population with exonuclease I.

10. (Previously presented) The method of claim 7, wherein said first member of a binding pair comprises biotin.